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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/155,676	01/04/99	WALLACH	D WALLACH=21

HM22/1109

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EXAMINER	
EPPS,J	
ART UNIT	**PAPER NUMBER**
1635	17

DATE MAILED: 11/09/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/155,676	David Wallach et al.
Examiner	**Group Art Unit**
Janet Epps	1635

☒ Responsive to communication(s) filed on *Aug 24, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *13-16, 20-26, 30, 32, 33, and 43-63* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☒ Claim(s) *13-16, 30, 43-49, 51-58, 60, 62, and 63* is/are allowed.

☒ Claim(s) *21-26, 32, 33, 50, 59, and 61* is/are rejected.

☒ Claim(s) *20* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Status of the Claims

1. The rejection of claims 13-16, 20-60 are withdrawn in response to Applicant's amendment and arguments filed 8/24/00.

2. Claims 27-29, 31, and 34-42 have been canceled by Applicant's amendment filed 8/24/00.

3. Claims 13-16, 20-26, 30, 32-33, and 43-60 are currently pending on the instant Application.

Response to Amendment

4. The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on 4/19/00 have been considered, and are approved by the Examiner.

5. The sequence lising provided by Applicants on 4/19/00 is technically acceptable and has been entered into the sequence database of the USPTO.

Claim Objections

6. Claim 20 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 20 does not further limit claim 53 since claim 53 is already limited to SEQ ID NO: 7.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 21-24, 26, 50, 59 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22, 26, and 50 recite the phrase "active fragment", this phrase is vague and indefinite since it is unclear what the claimed "active fragment" is a fragment of.

Claim 23, recite "a form suitable for", claims 23 and 24 recite the limitation "in the form of a suitable vector", and claim 26 recites the limitation "a suitable composition". These claims are vague and indefinite since neither the specification nor these claims clearly explain what constitutes "suitability". If the definition of the above term is merely that condition necessary to produce the intended result, the use of this term is redundant.

Claim 59 recites "a DNA sequence capable of binding to a sequence of (1) under moderately stringent conditions", this phrase is vague and indefinite since (1) is a polypeptide and not a DNA sequence.

Claim 61 , lines 5-6, and line 8, recite "a form suitable for", and it is not explained what constitutes suitability. If the definition of the above term is merely that condition necessary to produce the intended result, the use of this term is redundant.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 23-26, 32-33, and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modulation or mediation in cells of the activity of NF-kB *in vitro*, does not reasonably provide enablement for this practicing this method *in vivo* or for the modulation or mediation in cells of the activity of any other intracellular signaling activity modulated or mediated by TRAF2 *in vivo* or *in vitro*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 23-26, and 61 read on a method of gene therapy wherein the claimed method comprises introducing into cells a DNA sequence encoding said polypeptide in the form of a suitable vector carrying said sequence. Claims 32-33 read on a pharmaceutical composition for modulating the TRAF2 modulated/mediated effect on cells. Claim 32 in particular reads on compositions for use in gene therapy methods.

Applicant's specification fails to provide guidance to the skilled artisan on the parameters for gene delivery for the breadth of the claimed invention. Numerous factors complicate the gene

therapy art which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to, and the disease being treated.

Additionally, the specification does not provide any working examples which enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use genetic constructs which would result in the desired effect. Even assuming that an effective genetic material is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefit.

Recent reviews indicate that efficient delivery and expression of foreign DNA has not yet been achieved by any method. Marshall (*Science*, 269:1050-1055, August, 1995) states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1) and that "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field" (page 1054, column 3). James Wilson , one skilled in the art, is quoted in the Marshall article as saying

that "'[t]he actual vectors- how we're going to practice our trade- haven't been discovered yet" (page 1055, column 2). According to Anderson (1998), " Gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease. Several major deficiencies still exist including poor delivery systems, both viral and no-viral, and poor gene expression after genes are delivered." Orkin et al. (1995) state that " Daunting hurdles must be overcome if gene correction strategies are to achieve a meaningful clinical outcome.....Although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans." In addition, **In re Wands**, 858 F.d. 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations in determining whether or not undue experimentation would be involved in practicing inventions. These factors are: the quantity of experimentation necessary, the amount of direction or guidance needed, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, predictability or unpredictability of the art and the breadth of the claims. The amount of experimentation necessary to determine the appropriate delivery system of compositions for gene therapy to the correct tissues, and to determine a means to regulate the level of gene expression once the composition has reached its target which will be sufficient to correct the condition to be treated is beyond the scope of one with ordinary skill in the art.

In view of the lack of guidance provided in the specification of the instant application, the unpredictability in the art regarding gene therapy techniques, and the breadth of the given claims,

it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

Claims 23-26, 32-33, and 61 read on methods and compositions for modulation of the TRAF2 modulated or mediated effect on cells, however applicants have not demonstrated that they are able to control every possible effect that is mediated or modulated by TRAF2, applicant's specification clearly focuses on the aspect of TRAF2 mediation or modulation that involves the activity of NF-KB. Applicants have not demonstrated that TRAF2 is only capable of mediation or modulation by means of its interaction with NF-KB. To practice the instant method or use the claimed pharmaceutical compositions commensurate in scope with the claimed invention would involve determining all effects resultant from TRAF2 mediated or modulated activity in a cell and then using claimed compositions and methods to control these effects. The amount of experimentation necessary to determine the appropriate delivery system of the claimed compositions for controlling a TRAF2 mediated or modulated effect to the correct tissues, and to determine a means to regulate the level of the "effect" once the composition has reached its target which will be sufficient to modulate the "effect" is beyond the scope of one with ordinary skill in the art.

In view of the lack of guidance provided in the specification of the instant application, the unpredictability regarding determining all the "effects" or intracellular signaling activities that are mediated or modulated by TRAF2, and the breadth of the given claims, it is concluded that undue

experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

11. Claims 23, and 61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are drawn to methods of modulating or mediating the activity of any intracellular signaling activity modulated or mediated by TRAF2. The specification as filed does not describe any and all activities mediated or modulated by TRAF2, nor does the specification provide a sufficient description of all intracellular signaling molecules that may be modulated or mediated by TRAF2. The specification as filed focuses only on the specific activities of TRAF2 that are mediated by NF-KB. The activity of NF-KB alone is not representative of all possible intracellular signaling activities in a cell that is potentially mediated or modulated by TRAF2. The specification clearly fails to describe the claimed genus of intracellular signaling activities that are potentially mediated or modulated by TRAF2.

Therefore, the specification does not describe the claimed method in such full and concise terms so as to indicate that the applicant had possession of the claimed method at the time of filing of this application.

Allowable Subject Matter

12. Claims 13-16, 29, 30, 43-49, 51-58, 60, 62-63 are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps whose telephone number is (703) 308-8883. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet L. Epps, Ph.D.

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

November 6, 2000